Hepatitis C Virus new treatment and hemodialysis

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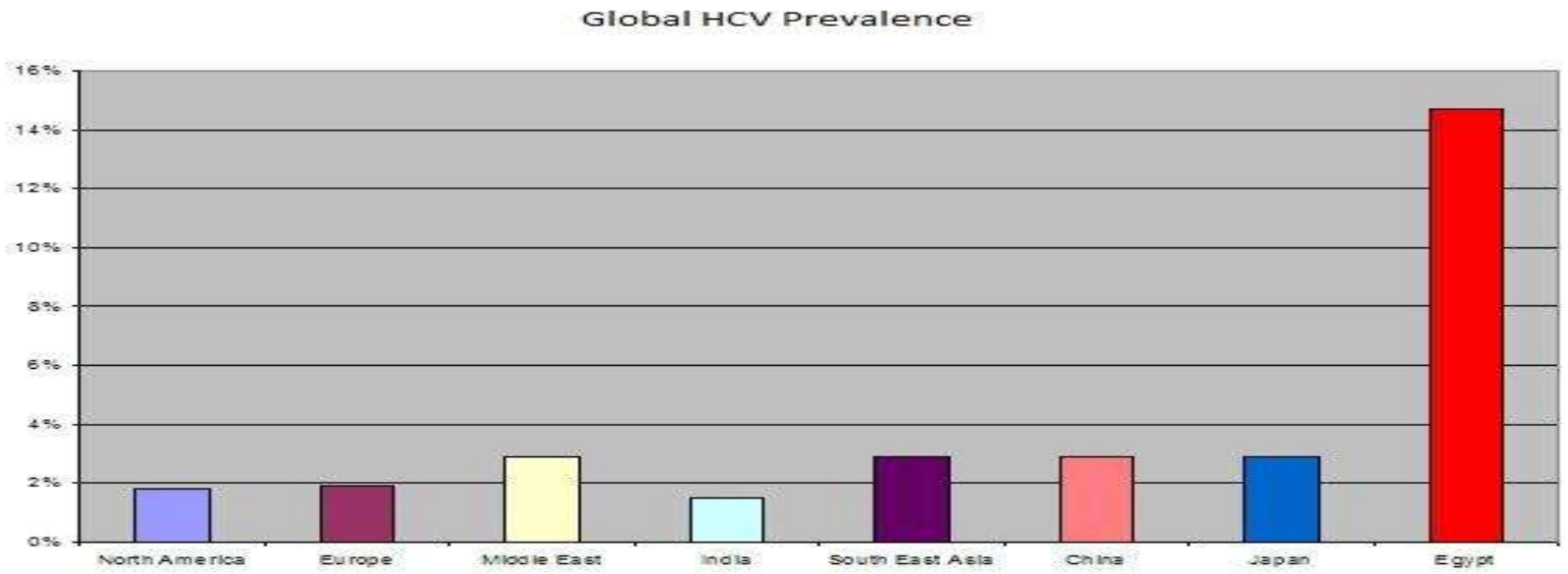
Hepatology and Gastroenterology

Mansoura University

Tanta, July 28th, 2016

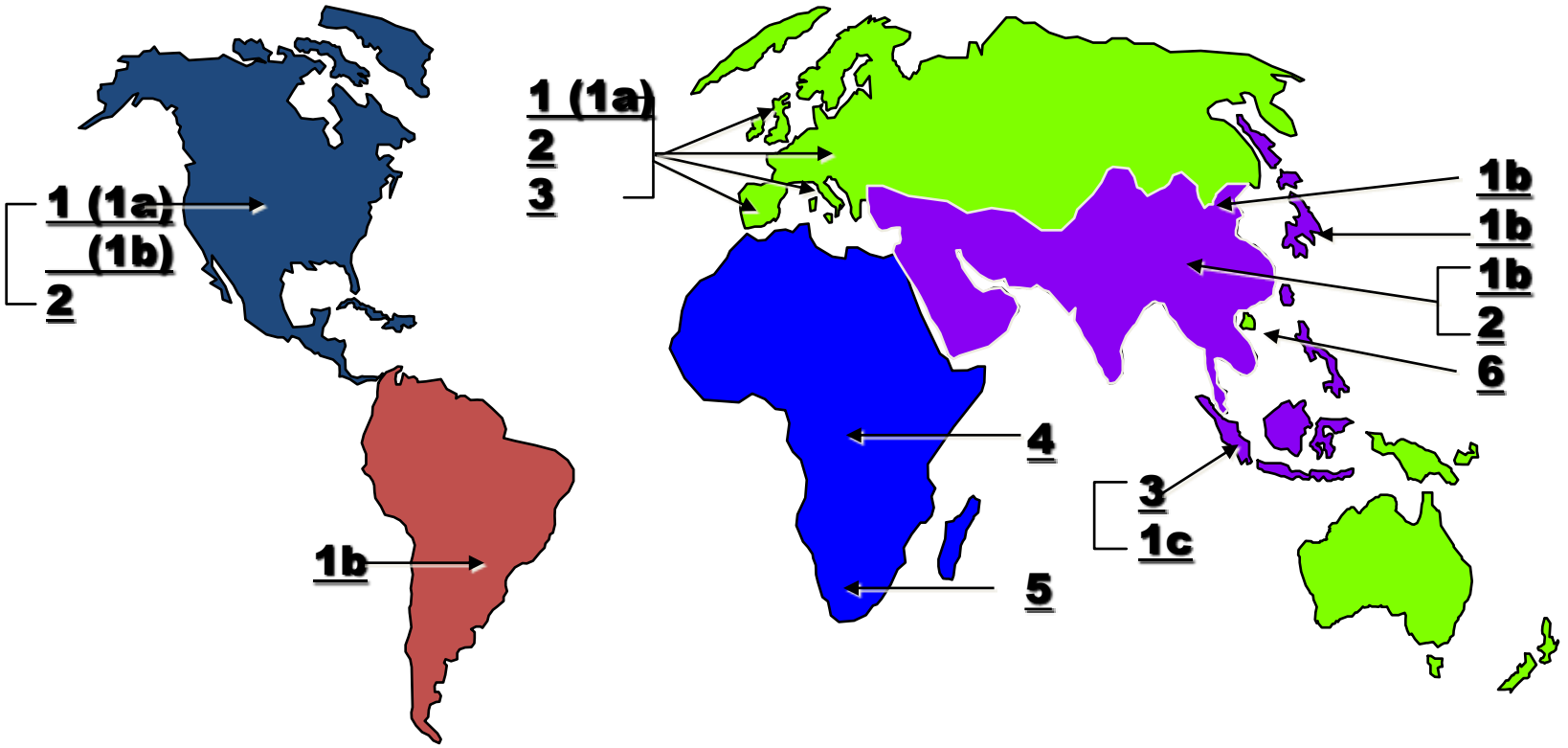
Hepatitis C Introduction

- WHO estimates that about 3% of the world's population are infected with HCV.
- Egypt has the highest prevalence of hepatitis C virus (HCV) in the world, estimated nationally at 14.7%.
- The Most common type is HCV genotype 4 (≥ 90 %)



WHO
BMC Infect Dis. 2013 Jun 24;13:288. doi: 10.1186/1471-2334-13-288

Worldwide Distribution of Genotypes



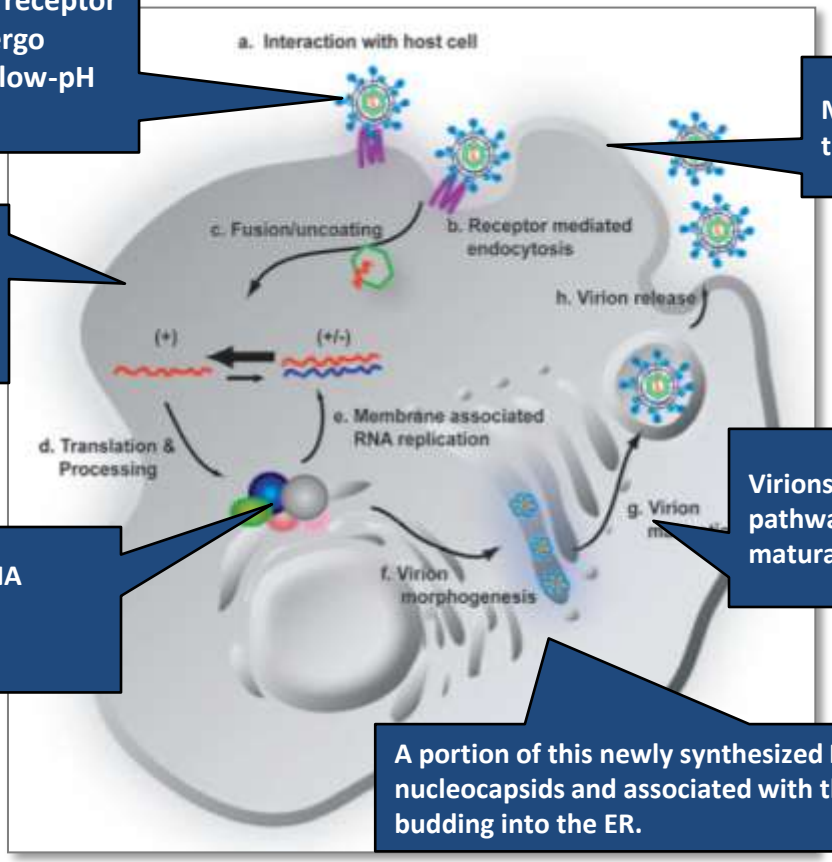
The Lifecycle of HCV

Unlike HIV and HBV, HCV is Unable to Integrate Into the Host Genome and Can Thus Be Cured

Extracellular HCV virions interact with receptor molecules at the cell surface and undergo receptor-mediated endocytosis into a low-pH vesicle.

The viral RNA is released into the cytoplasm and translated to generate a single large polyprotein that is processed into the 10 mature HCV proteins.

The mature HCV proteins replicate the RNA genome via a minus-strand replicative intermediate to produce progeny RNA.



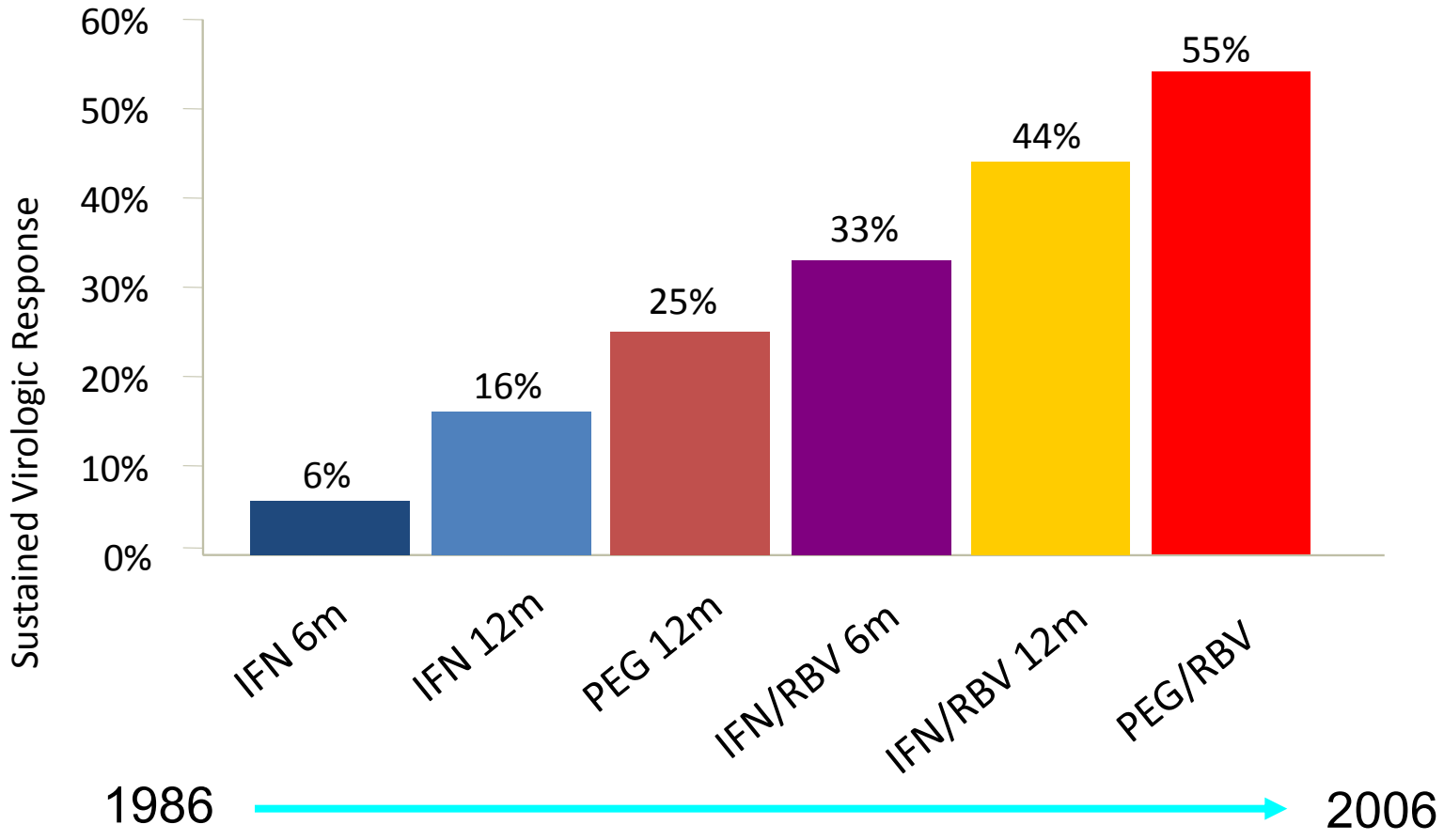
Mature virions are released from the cell, completing the life cycle.

Virions follow the cellular secretory pathway and, during this transit, maturation of particles occurs.

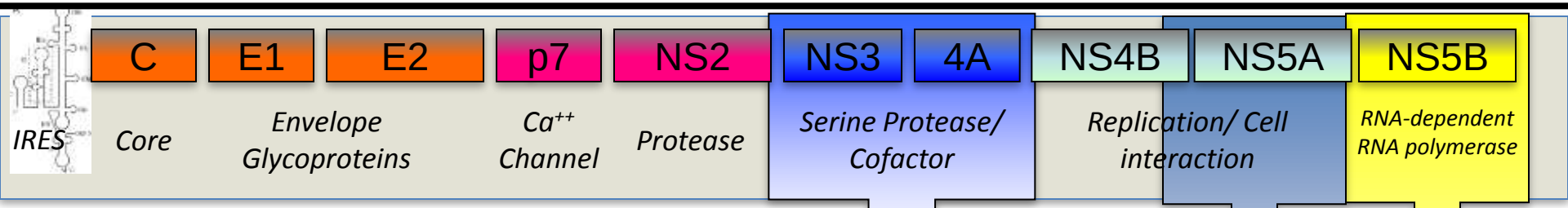
A portion of this newly synthesized RNA is packaged into nucleocapsids and associated with the HCV glycoproteins, leading to budding into the ER.

J Virol. 2007 September; 81(17): 8853–8867.

Progress in achieving sustained viral response in chronic hepatitis C with IFN-based regimens



DAA Agents Overview



Mod to High potency
+/-Multi-genotypic coverage
Intermediate barrier to resistance

Telaprevir, Boceprevir, Simeprevir, Faldaprevir, Asunaprevir, Paritaprevir

Daclatasvir
Ledipasvir
Ombitasvir
Veltapasvir
Elbasvir
TD-6450

High potency
Multi-genotypic coverage
Low barrier to resistance

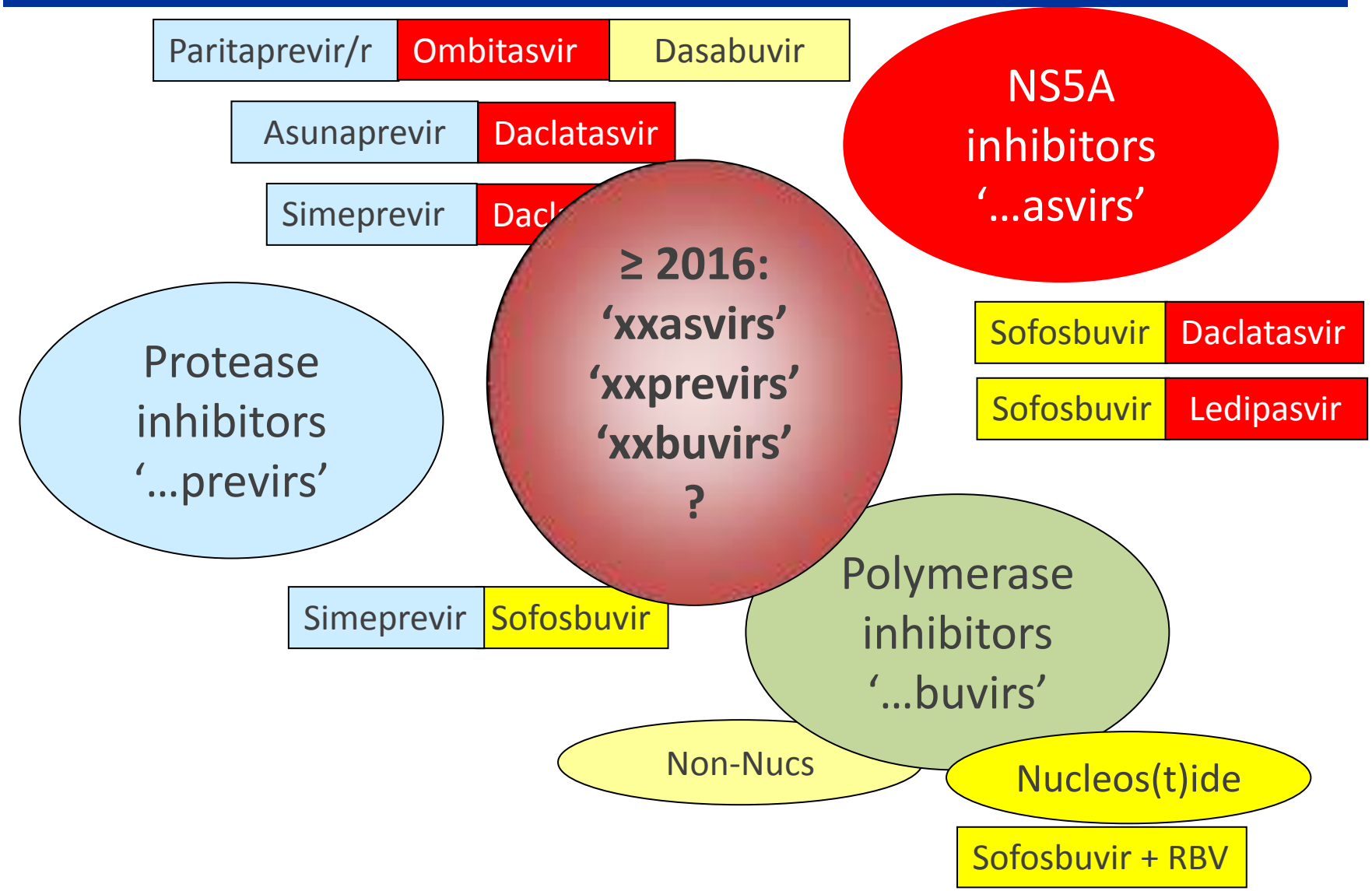
NS5B Non Nucleoside Inhibitors (NNI)
Low potency
Limited-genotypic coverage
Low barrier to resistance

Deliobuvir, Dasabuvir, BMS-791325

NS5B Nucleotide Inhibitors (NI)
Intermediate to high potency
Pan genotypic coverage
High barrier to resistance

Sofosbuvir

IFN-free regimens available in 2016



EASL Recommendations 2015, DOI: http://dx.doi.org/10.1016/j.jhep.2015.03.025. Accessed April 2015.

2013


Pegasys®
peginterferon alfa-2a
180 micrograms / 0.5 ml solution for injection
1 pre-filled syringe - 0.5 ml /
injection needle
Roche


Peg-Intron*
Schering-Plough


Ribavirin Capsules
4 Capsules
Ribavin 200
FINNACLE

2014


NDC 61958-1501-1 28 tablets
Sovaldi™
(sofosbuvir) Tablets
400 mg


OLYSIO 150 mg
hard capsules
simeprevir
oral use
7 hard capsules
janssen


Olysio
(simeprevir) Capsules
150 mg
Hepatitis C Online

2015


Daklinza
60 mg
film-coated tablets
daclatasvir
Oral use
28 x 1 film-coated tablet

2016


viekira pak™
Tear strip below to open
TEAR HERE
OPEN
AM
PM
MON
TUE
WED
THU


viekira pak™
DAILY TREATMENT INSTRUCTIONS
AM
PM
Take with food
Take with food
Push down on tablets breaking through back side

2016


NDC 0074-3082-28
Rx only
technivie™
ombitasvir, paritaprevir, ritonavir tablets 12.5 mg / 75 mg / 50 mg
Each tablet contains ombitasvir, paritaprevir, ritonavir 12.5 mg / 75 mg / 50 mg


technivie®
DAILY TREATMENT INSTRUCTIONS
Take + food
Take with food
Push down on tablets breaking through back side
LIFT HERE

2016


Viekirax®
12,5 mg / 75 mg / 50 mg
filmdragerade tabletter /
kalvopäällysteiset tabletit
ombitasvir / paritaprevir / ritonavir
ombitasviiri / paritapreviiri / ritonaviiri
För oral användning / Suun kautta
14 filmdragerade tabletter /
14 kalvopäällysteistä tablettia
Del av ett multipack; kan inte säljas separat.
Osa monipakkausta; ei voida myydä erikseen.

2016


Qurevo®
12.5 mg / 75 mg / 50 mg
film-coated tablets
ombitasvir / paritaprevir / ritonavir
28 film-coated tablets

Paritaprevir/ritonavir/ombitasvir + dasabuvir

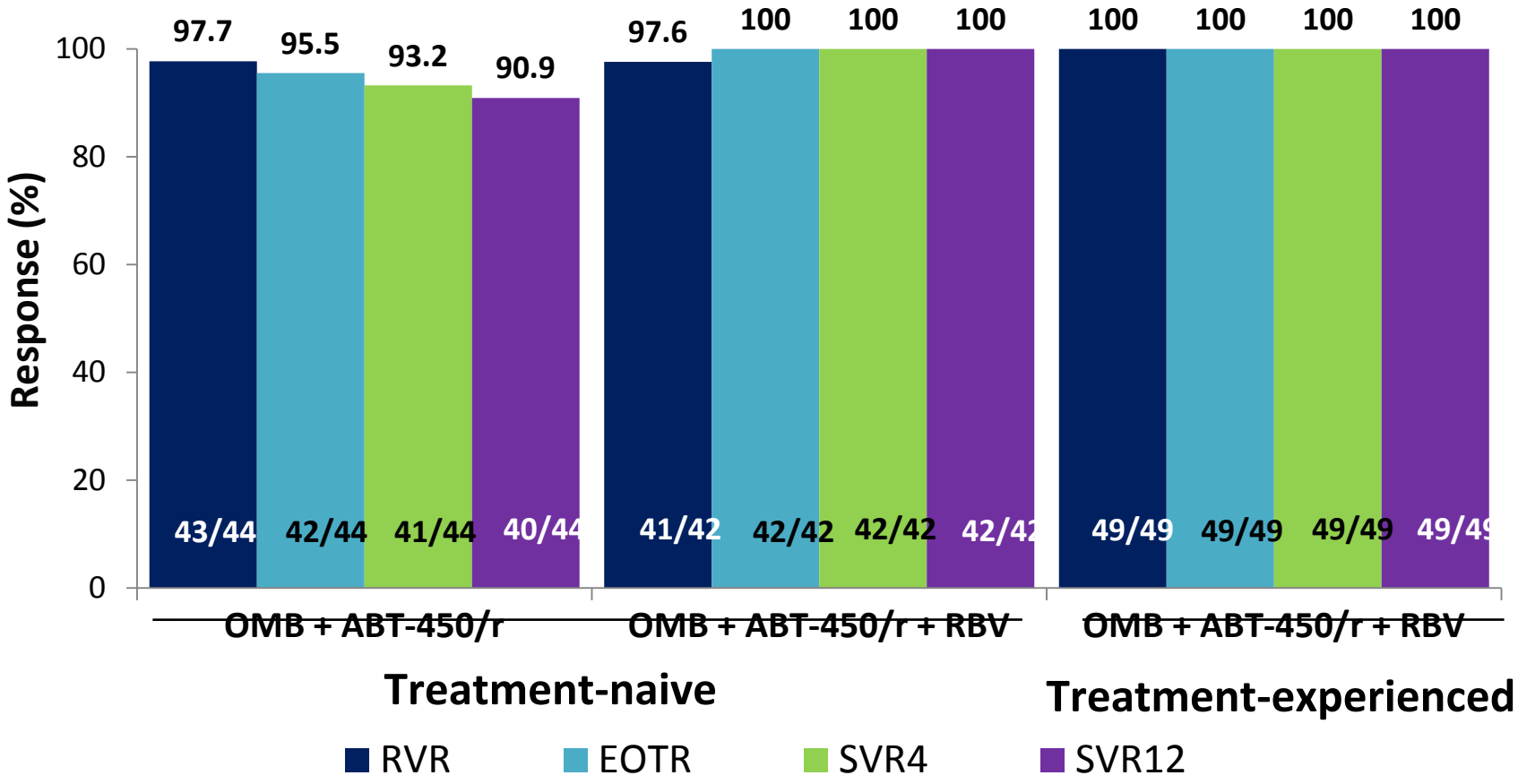
- the daily fixed-dose combination of:
  - Paritaprevir (150 mg).
  - Ritonavir (100 mg).
  - Ombitasvir (25 mg).
  - Dasabuvir (250 mg).

- In October 2015, the FDA released a warning regarding the use of the PrOD or PrO (without dasabuvir) in patients with cirrhosis.

FDA, 2015

OMB + PARIT/RIT ± RIB IN GENOTYPE 4(PEARL-I)

- **135 GT4 patients** have been enrolled in **PEARL -1 Trial**, The response rate (SVR12) and EOTR were 100% among all pegIFN/RBV-naïve and all pegIFN/RBV-experienced patients who were treated with 2DAAs + RBV, and >90% in all treatment-naïve patients treated with 2DAAs without RBV



Pol S, et al. AASLD 2014, Boston. #1928

2016


Harvoni®
(ledipasvir, sofosbuvir) Tablets
90 mg / 400 mg
Note to pharmacist:
Do not cover ALERT box with pharmacy label.
ALERT: Find out about medicines that should NOT be taken with Harvoni®
GSI

Ledipasvir/sofosbuvir

- The fixed-dose combination of ledipasvir (90mg) and sofosbuvir (400 mg)
- The overall response rate is 98 %
- Generally safe with no severe side effects.

?????????


NOW APPROVED
ZEPATIER™
(elbasvir and grazoprevir)
50 mg/100 mg tablets
MERCK

?????????


Zepatier
(elbasvir and grazoprevir) tablets
50 mg/100 mg
Rx only
14 Tablets

?????????


MERCK

Liverpool HEP iChart

- **The University of Liverpool provided this service with summary data of hepatitis drug interactions.**
- **Full details are available at:**

www.hep-druginteractions.org

INTERNATIONAL GUIDELINES

Patients with chronic HCV without cirrhosis

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	8-12 wk, without RBV	12 wk with RBV	No	12 wk without RBV	12 wk without RBV
Genotype 1b					12 wk without RBV			
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV
Genotype 4	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk without RBV	No	No	No	12 weeks without RBV

Treatment-naïve patients and patients who failed a treatment based on pegIFN +RBV.

EASL Recommendations 2015, DOI: http://dx.doi.org/10.1016/j.jhep.2015.03.025. Accessed April 2015.

Patients with chronic HCV without cirrhosis

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 4	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV

aTreatment-naïve patients and patients who failed a treatment based on pegIFN +RBV.

EASL Recommendations 2015, DOI: http://dx.doi.org/10.1016/j.jhep.2015.03.025. Accessed April 2015.

EASL Recommendations 2015

patients with chronic HCV with compensated (CP-A) cirrhosis

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

aTreatment-naïve patients and patients who failed a treatment based on pegIFN +RBV.

EASL Recommendations 2015, DOI: http://dx.doi.org/10.1016/j.jhep.2015.03.025. Accessed April 2015.

patients with chronic HCV with compensated (CP-A) cirrhosis

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 4	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV

Treatment-naïve patients and patients who failed a treatment based on pegIFN +RBV.
EASL Recommendations 2015, DOI: http://dx.doi.org/10.1016/j.jhep.2015.03.025. Accessed April 2015.

IFN-Free Options, Gen 4

	SOF/LDV	O/P/R	SOF + SIM	SOF + DCV
No cirrhosis	**12 wk without RBV**	**12 wk with RBV**	**12 wk without RBV**	**12 wk without RBV**
Compensated cirrhosis (CPT-A)	**12 wk with RBV, or 24 wk without RBV***	**24 wk with RBV**	**12 wk with RBV, or 24 wk without RBV***	**12 wk with RBV, or 24 wk without RBV***
Decompensated cirrhosis (CPT-B and CPT-C)	**12 wk with RBV, or 24 wk without RBV***	**No**	**No**	**12 wk with RBV, or 24 wk without RBV***

*Patients with negative predictors of response can be treated 24 weeks with ribavirin (negative predictors: treatment-experienced, platelet <75x10^3/uL)

American Association for the Study of Liver Diseases

AASLD

IDSA

Infectious Diseases Society of America

Genotype Recommended Alternative NOT Recommended

AASLD-IDSA RECOMMENDATIONS FOR TESTING,MANAGING, AND TREATING ADULTS INFECTED WITH HEPATITIS C VIRUS

- Authors On behalf of the Hepatitis C Guidance Panel (see AASLD/IDSA HCV GUIDANCE PANEL MEMBERS AND AUTHORS)

February 24, 2016

GUIDELINES FOR THE SCREENING, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS C INFECTION

UPDATED VERSION

APRIL 2016

GUIDELINES

PATIENTS WITH RENAL IMPAIRMENT

Renal patients are overexposed to hepatitis C virus (HCV) infection. Hepatitis C virus infection impacts general outcomes in chronic kidney disease, dialysis or transplanted patients.

Infectious Diseases and Therapy. First Online: 07 July 2016

the Dialysis Outcomes and Practice Patterns Study (DOPPS)

In 2004, DOPPS published the largest study analyzing the HCV serological status in 8615 randomly selected hemodialysis patients treated in 308 dialysis facilities (in 8 countries in Europe, HCV USA and Japan). It showed the HCV antibody prevalence to be 14.7%.

Kidney Int. 2004;65(6):2335–42.

Table 1: HCV prevalence, by DOPPS region/country and phase in initial cross-section of each phase

Region/Country	DOPPS Phase 1	2	3	4	5	p-value for trend[b]
Australia-New Zealand	-	7.4 (513)	5.0 (519)	5.2 (449)	3.8 (393)	0.86
Belgium	-	6.1 (537)	5.1 (503)	4.6 (542)	4.0 (485)	0.08
Canada	-	4.9 (599)	4.5 (546)	5.6 (425)	4.0 (457)	0.69
China		-	-	14.0 (1379)	9.9 (1189)	
France	14.3 (540)	16.0 (510)	10.2 (549)	6.9 (501)	-	<.01
GCC-6[c]	-	-	-	-	19.3 (910)	
Germany	4.2 (505)	4.2 (566)	3.8 (577)	2.9 (586)	4.5 (584)	0.20
Italy	23.1 (561)	21.8 (576)	17.0 (521)	9.2 (623)	11.4 (485)	<.01
Japan	19.0 (2155)	14.3 (1782)	12.4 (1822)	9.4 (1574)	11.0 (1609)	<.01
Russia	-	-	-	-	13.7 (486)	
Spain	21.4 (491)	11.8 (600)	9.1 (663)	8.7 (674)	8.9 (613)	<.01
Sweden	-	4.9 (547)	5.0 (539)	4.6 (531)	6.0 (426)	0.79
Turkey	-	-	-	-	6.6 (383)	
United Kingdom	2.4 (493)	3.0 (553)	1.2 (443)	2.1 (439)	4.4 (397)	0.50
United States[d]	11.7 (3156)	8.2 (2238)	6.3 (1799)	5.9 (4412)	7.4 (2977)	<.01
All DOPPS countries	14.2 (7901)	9.6 (9021)	7.8 (8481)	7.4 (12135)	9.5 (11394)	

HCV prevalence by phase shown as % (n patients)

a. DOPPS phase 1 (1996-2001 in the United States, 1998-2001 in Europe/Japan); phase 2 (2002-2004); phase 3 (2005-2008); phase 4(2009-2011); phase 5 (2012-2014)
b. Phase included as a linear term in a logistic model with HCV+ (vs. HCV-) as the outcome, accounting for facility clustering and adjusted for age, male sex, years on dialysis
c. Gulf cooperation council countries – includes Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates
d. HCV prevalence consistently higher in US-black patients: 15.8% vs. 8.8% in DOPPS phase 1, 12.4% vs. 6.1% in phase 2, 10.9% vs. 3.7% in phase 3, 10.7% vs. 3.9% in phase 4, 10.1% vs. 6.3% in phase 5.

Brian Bieber[1], David A. Goodkin[1], Chizoba Nwankwo[2], Jean Marie Arduino[2], Takashi Akiba[3], Michel Jadoul[4], Ronald L. Pisoni[1]

[1]Arbor Research Collaborative for Health, Ann Arbor, MI, United States; [2]Merck & Co., Inc., Kenilworth, NJ, United States; [3]Department of Blood Purification and Internal Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan; [4]Université Catholique de Louvain, Brussels, Belgium

Abstract ERA-EDTA London 2015

Prevalence of HCV Infection in Dialysis Patients

- **60 to 100 % in Egypt**
- **8 to 36 % in North America**
- **1 to 54 % in Europe**
- **17 to 51% in Asia**
- **1.2 to 10% in New Zealand and Australia**

Hussein El-Fishawy et al. 2016

Cr Cl 30 - 80 mL / min

- **No dosage adjustment is required when using:**

- **Daclatasvir.**
- **Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg).**
- **Fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg).**

  Rating: Class I, Level A

AASLD-IDSA guidelines, February 24th, 2016

An active metabolite of sofosbuvir is actively renally secreted, and therefore overexposure may be observed in CKD patients.

Sofosbuvir is used at a 400-mg daily dosage in patients with GFR above 30 ml/min/1.73 m2.

The authors tested a full dose or half dose of sofosbuvir in stage 4 or 5 patients (on dialysis or not) despite the exclusive renal elimination pathway.

Nazario HE et al. Liver Int. 2016;36(6):798–801.

Cr Cl < 30 mL / min or ESRD

- **When the urgency to treat is high and kidney transplant is not an immediate option:**

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100mg) for 12 weeks is a Recommended regimen.**

  Rating: Class IIb, Level B

AASLD-IDSA guidelines, February 24th, 2016

The grazoprevir/elbasvir combination, with or without ribavirin, was recently approved by the FDA for the treatment of chronic HCV genotype 1 and 4 infections in patients with end-stage renal disease on hemodialysis.

No drug dosage adaptation in case of renal failure.

Infectious Diseases and Therapy. First Online: 07 July 2016

?????????


NOW APPROVED
ZEPATIER™
(elbasvir and grazoprevir)
50 mg/100 mg tablets
MERCK

Cr Cl < 30 mL / min or ESRD

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with RBV at reduced doses (200 mg thrice weekly to daily*) for 12 weeks is an Alternative regimen.**
- **Caution is recommended due to the potential for hemolytic anemia due to impaired renal clearance and RBV should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.**

  Rating: Class IIb, Level B
- RBV should be discontinued if hemoglobin level declines by more than 2 g/dL despite the use of erythropoietin.

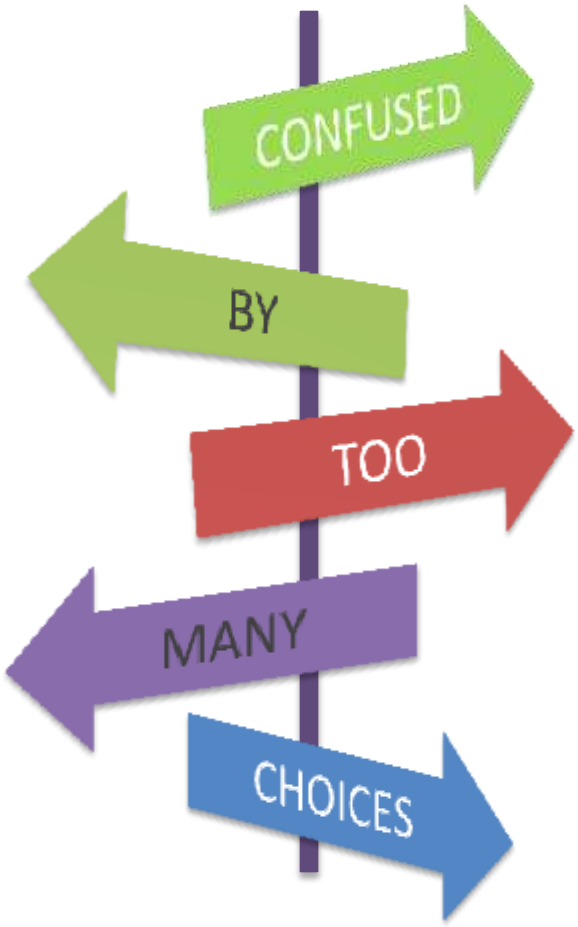
AASLD-IDSA guidelines, February 24th, 2016

Recommended for patients after kidney transplantation

- **Sofosbuvir (400 mg)/ Daclatasvir (60 mg).**
- **Sofosbuvir (400 mg)/ Ledipasvir (90 mg).**

Transplant International 2016

Treatment of HCV G4 in 2016: already too many options?



TOUGH DECISIONS AHEAD

RBV: yes/no?

How long to treat?

Which drugs to use?

How to treat GT-3?

Advanced liver disease?

When to start treatment?

DDI profile

Impaired renal function?

Resistance?

Selected articles

1

Efficacy of Direct-Acting Antiviral Combination for Patients With Hepatitis C Virus Genotype 1 Infection and Severe Renal Impairment or End-Stage Renal Disease

- 20 patients were given ombitasvir co-formulated with paritaprevir and ritonavir DAAs.
- Drugs were well tolerated.
- All 20 patients completed 12 weeks of treatment. Eighteen of the 20 patients achieved SVR12 (90%).

Gastroenterology 16 April 2016

2

Therapy of hepatitis C by direct-acting anti-virals: the end of HCV in dialysis population?

- patients with HCV genotype 1 and chronic kidney disease stage 4 or 5 were given the 3D regimen.
- Treatments were generally well tolerated.
- All patients completed treatment with 100% viral response (14/14) but data on sustained viral response are under evaluation.

Expert Review of Clinical Pharmacology; 2015

In conclusion

Drug Choices Need to Be Guided by Safety in Patients With Renal Impairment

DAA	Primary Metabolic Pathway	Predicted Need for Dose Adjustment if eGFR<15 ml/min or HD	Recommendations Per Package Insert
Sofosbuvir	**Renal**	**Unknown**	**Not if CrCl < 30 mL/min**
Ledipasvir	Hepatic	Probably not	Unknown
Daclatasvir	Hepatic	Not required	
Simeprevir	Hepatic	Probably not	Not if CrCl < 15 mL/min
Paritaprevir/r	Hepatic	Not required	No dose adjustment for mild→severe renal impairment Not studied in HD patients
Ombitasvir	Hepatic		
Dasabuvir	Hepatic		
Ribavirin	**Renal**	**Yes**	**Yes, at reduced doses**

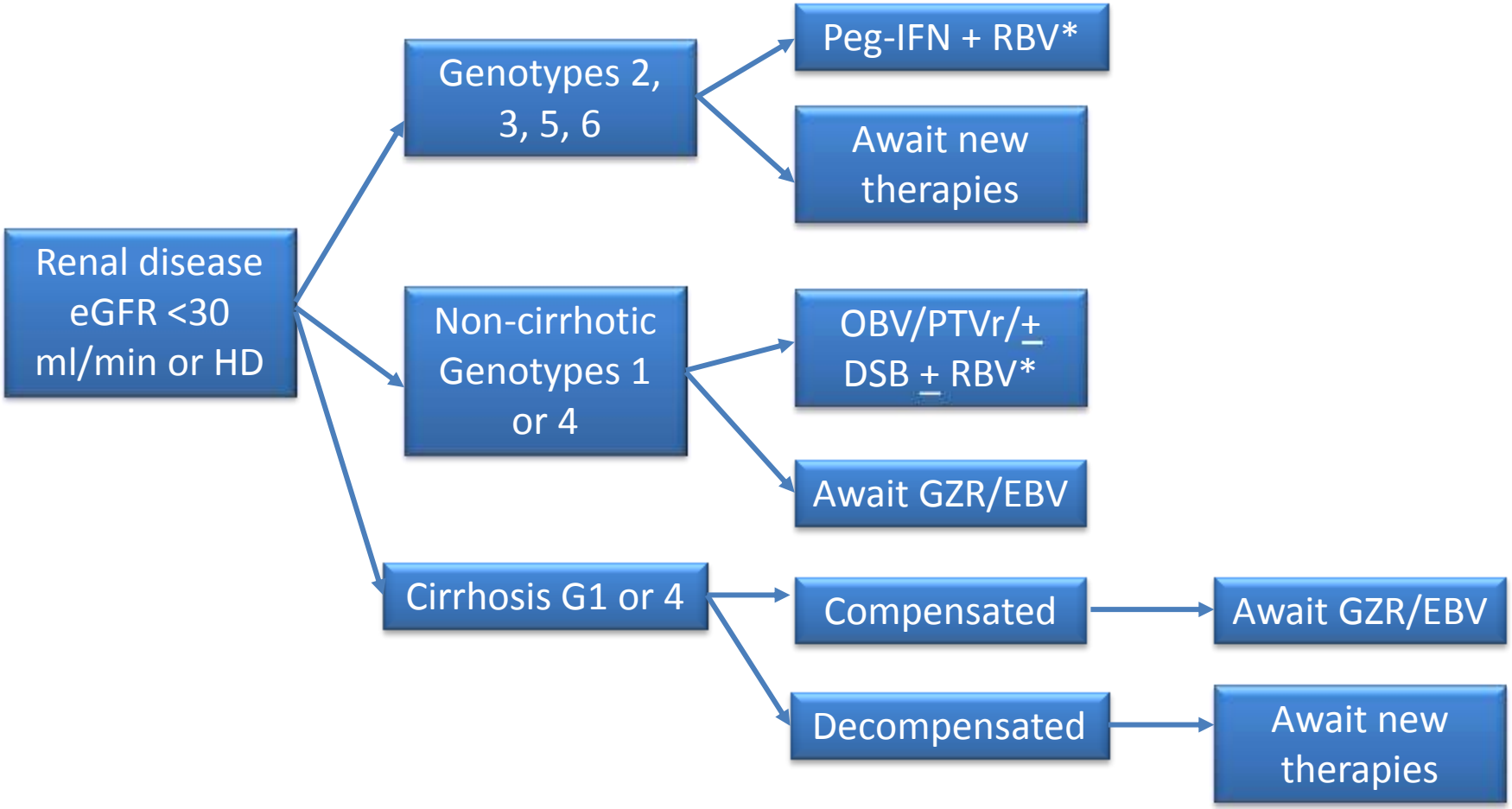
Maruyama A, Nephrol Dial Transplant 2015

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Management Options for ESRD (CrCl <30 ml/min)



*Only if non-cirrhotic and treatment is urgent and renal transplant not immediately available

www.hcvguidelines.org accessed Sept 11,2015 with NT adaptation

Most "special populations" have DAA treatment options.

Most of them enjoy excellent outcomes (SVR).

Persons with ESRD represent the largest group with unmet need.

Economist Intelligence Unit

The Economist

THE SILENT PANDEMIC

TACKLING HEPATITIS C WITH POLICY INNOVATION

A report from the Economist Intelligence Unit.

Case study

HCV in the developing world: Close-up on Egypt

Egypt's HCV problem i
greater than that of ar

For F DeWolfe Miller, professor of epidemiology at Hawaii University and an expert on Egyptian public health and the HCV pandemic, the spread of the disease there is "nothing short of a scandal".

carriers, the legacy of a disastrous pu
programme launched in the 1950s to
the population against the river-bor
bilharzia. Recent epidemiological stu
individual communities have demonstrated a
close link between the advent of the vaccine –

care," he says. "Almost every pharmacy, doctor
and dental office in the country needs to clean

Although Egypt now has the world's largest HCV treatment programme – and in October 2012 launched what will be the world's most comprehensive national HCV patient registry-every year at least 500,000 new HCV infections occur.

ller adds: "Egypt has one of the
rgest medical education systems in
ey have all heard of Semmelweis,
an doctor who discovered that
g reduces mortality, but they don't
made the connection. Unless that
aken on board, it is going to be a
fore anything changes there."

Curing Chronic Hepatitis C — The Arc of a Medical Triumph

Raymond T. Chung, M.D., and Thomas F. Baumert, M.D.


BCE ECB EZB EKT EKP 2002

Hepatitis C

« Now is this the end…???

« Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning »

Winston Churchill

THANK YOU